



CHARLES UNIVERSITY
Faculty of Pharmacy
in Hradec Králové

Extending a pharmacodynamic model for nuclear receptor-induced enzyme production with spatial resolution

Jurjen Duintjer Tebbens

joint work with

Martin Lanzendörfer, Ctirad Matonoha, Štěpán Papáček

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Compartmental models

The traditional approach to compute the therapeutic effect of drugs is by usage of a **compartmental model**.

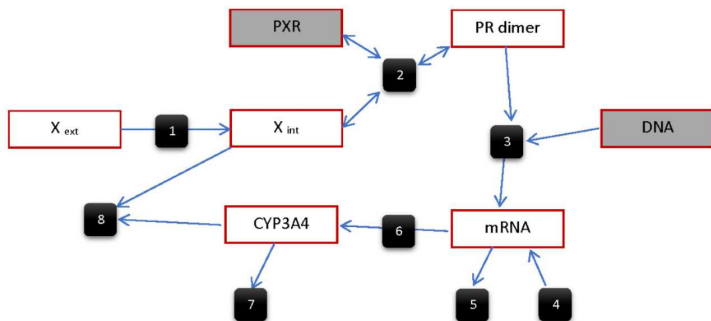
It divides the part of the body to be studied in **compartments** in which the concentrations of the involved substances (drugs, receptors, metabolizing enzymes) are assumed to be *homogeneously* distributed.

Examples of compartments include the blood circulatory system, intracellular and extracellular fluid, adipose tissue, organs, cells, but they can represent abstract units as well.

Compartmental models are particularly suited for drugs binding to membrane receptors and very popular in physiologically based pharmacokinetic (PBPK) models for clinical pharmacy.

But they are employed as well for the more complicated behavior of nuclear receptors:

A model for ligand-binding to the nuclear PXR receptor



Luke N.S., DeVito M.J., Shah I., El-Masri H.A.:

Development of a quantitative model of pregnane X receptor (PXR) mediated xenobiotic metabolizing enzyme induction.

Bulletin of mathematical biology, vol. 72(7), p. 1799-1819 (2010).

A model for ligand-binding to the nuclear PXR receptor

$$\frac{dX_{\text{ext}}(t)}{dt} = d(t) - k_{\text{imp}} X_{\text{ext}}(t) + k_{\text{exp}} X_{\text{int}}(t)$$

$$\frac{dX_{\text{int}}(t)}{dt} = k_{\text{imp}} X_{\text{ext}}(t) - k_{\text{exp}} X_{\text{int}}(t) - k_{\text{assoc}} X_{\text{int}}(t) (S_{\text{PXR}} - \text{PR}(t)) - k_{\text{met}} \text{CYP3A4}(t) X_{\text{int}}(t) + k_{\text{dis}} \text{PR}(t)$$

$$\frac{d\text{PR}(t)}{dt} = k_{\text{assoc}} X_{\text{int}}(t) (S_{\text{PXR}} - \text{PR}(t)) - k_{\text{dis}} \text{PR}(t)$$

$$\frac{d\text{mRNA}(t)}{dt} = k_{\text{mRNA}} \text{PR}(t) - k_{\text{mRNA,deg}} \text{mRNA}(t) + p_{\text{mRNA,back}}$$

$$\frac{d\text{CYP3A4}(t)}{dt} = k_{\text{cyp}} \text{mRNA}(t) - k_{\text{cyp,deg}} \text{CYP3A4}(t)$$

with variables (substance concentrations)

X_{ext} = Xenobiotic concentration outside the cell

X_{int} = Xenobiotic concentration inside the cell

PR = PXR/RXR heterodimer concentration

mRNA = mRNA concentration

CYP3A4 = CYP3A4 concentration

A model for ligand-binding to the nuclear PXR receptor

and where

$d(t)$	=	time-dependent dosing function
k_{imp}	=	first order import constant for the xenobiotic
k_{exp}	=	first order export constant for the xenobiotic
k_{assoc}	=	association rate constant for PXR/RXR heterodimer formation
S_{PXR}	=	the total system PXR concentration (binded and free)
k_{met}	=	second order metabolic constant
k_{dis}	=	first order dissociation constant
k_{mRNA}	=	first order transcription rate constant for mRNA
$k_{mRNA,deg}$	=	first order degradation coefficient for mRNA
$p_{mRNA,back}$	=	background production rate for mRNA
k_{cyp}	=	first order translation rate constant for CYP3A4
$k_{cyp,deg}$	=	first order degradation coefficient for CYP3A4

Pharmacodynamic models

The systems of ODE's result from the assumed physical and chemical properties of the involved processes and are often **stiff**.

The compartmental modeling procedure has been used for decades. Dedicated PBPK software exists: CellDesigner, ADAPT, Simcyp, NONMEM.

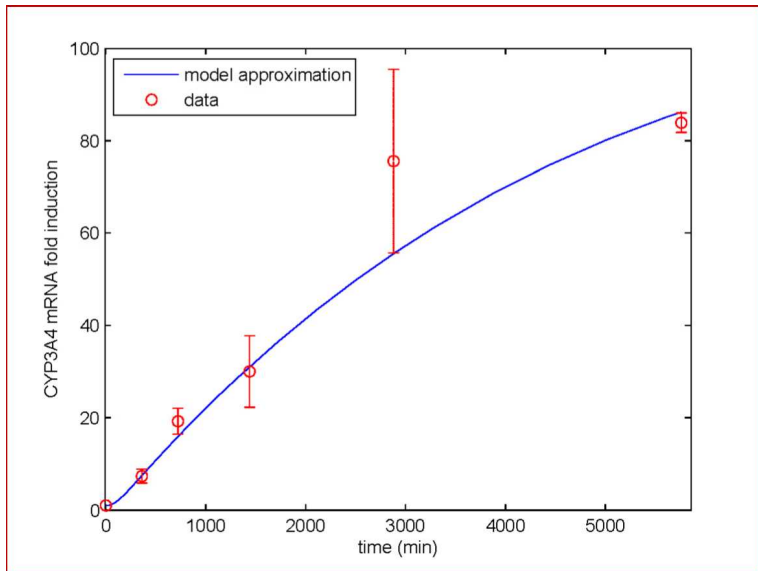
PBPK models can be highly sophisticated multi-compartmental models for the action of several substances, including *feedback loops and drug-drug interaction*. Repeated dosing can be simulated as well by extension of the initial conditions.

Many pharmacologic phenomena can be modelled *as long as we know the correct equations for the underlying processes and the correct values of the involved parameters!*

Typically, only part of the **model's parameters** is known from literature or obtainable from direct experimental measuring. Parameter estimation is an integral part of the modeling process itself. It is done through collecting of *in vitro* or *in vivo* data from donors and subsequent **curve fitting**.

Curve fitting (mostly sum of squares minimization or maximum likelihood estimation) represents constrained optimization: the desired parameters are mostly positive and must lie in physically meaningful intervals. In fact, the parameter estimation problems may be ill-posed and **regularization** may be necessary. Sometimes a sensitivity analysis is performed.

A PBPK model for the action of Rifampicin



Parameter estimation

The parameter estimation makes the computational costs significantly more expensive:

- The iterative optimization process requires *repeated* computation of the ODE model.
- Thus in fact a *sequence* of systems of ODE's needs to be solved.
- Efficient optimization procedures therefore have a large impact on total costs.

Modeling and parameter estimation are often alternated for iterative refinement.

Models can be very (experimental) data-driven. In addition to parameter fitting there is a tendency to perform *model fitting* as well, when the underlying biophysical processes are not understood or too complicated.

For example, delay of substance transport is sometimes modeled, without knowledge of its biophysical cause or its location, through artificially increasing the number of compartments (defining so-called *transit compartments*).

This is one motivation for including **spatial resolution**.

Spatial resolution?

Further reasons to add **spatial resolution** to the models could be:

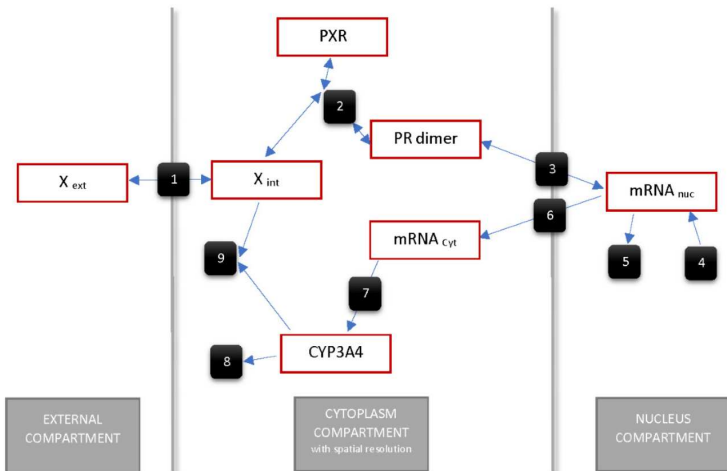
- In some clinical applications spatial information is indispensable, for instance when the drug is efficient only if it reaches very precise organ locations (e.g. the retina for eye diseases).
- Because elevated drug concentrations are often **toxic**, it is crucial to monitor not only the average drug level all over a compartment, but to detect possible localized maxima as well. Similarly, approaching the so-called no-observed-adverse-effect levels should be detectable locally, inside compartments.
- In other applications, spatial resolution may not seem necessary at first sight, but might reveal unexpected explanations for observed pharmacological phenomena.

While substances can often be assumed to be homogeneously distributed, it would be beneficial to provide spatial resolution in those compartments, where physiological properties or observations suggest heterogeneous distributions.

Mathematically this leads to a **mixed system of PDEs coupled with ODEs**.

For the above Rifampicin model, we may assume that the most interesting localized reactions take place in the cytoplasm and consider the following coupling:

A mixed PDE/ODE model



A mixed PDE/ODE model for the action of Rifampicin

$$v_{\text{ext}} \frac{dX_{\text{ext}}(t)}{dt} = d(t) - k_{\text{imp}} X_{\text{ext}}(t) + \frac{k_{\text{exp}}}{\sigma_{\text{ext}}} \int_{\Gamma_{\text{ext}}} X_{\text{int}}(t, x) dS$$

$$\begin{aligned} \partial_t X_{\text{int}}(t, x) = & D_{\text{int}} \Delta X_{\text{int}}(t, x) - k_{\text{assoc}} X_{\text{int}}(t, x) \text{PXR}(t, x) \\ & - k_{\text{met}} \text{CYP3A4}(t, x) X_{\text{int}}(t, x) + k_{\text{dis}} \text{PR}(t, x) \end{aligned}$$

$$\partial_t \text{PXR}(t, x) = D_{\text{PXR}} \Delta \text{PXR}(t, x) - k_{\text{assoc}} X_{\text{int}}(t, x) \text{PXR}(t, x) + k_{\text{dis}} \text{PR}(t, x)$$

$$\partial_t \text{PR}(t, x) = D_{\text{PR}} \Delta \text{PR}(t, x) + k_{\text{assoc}} X_{\text{int}}(t, x) \text{PXR}(t, x) - k_{\text{dis}} \text{PR}(t, x)$$

$$\begin{aligned} \frac{d \text{mRNA}_{\text{nuc}}(t)}{dt} = & \frac{k_{\text{mRNA}, \text{nuc}}}{\sigma_{\text{nuc}}} \int_{\Gamma_{\text{nuc}}} \text{PR}(t, x) dS - k_{\text{mRNA}, \text{deg}} \text{mRNA}_{\text{nuc}}(t) \\ & + p_{\text{mRNA}, \text{back}} + k_{\text{nuc}} \left(\frac{1}{\sigma_{\text{nuc}}} \int_{\Gamma_{\text{nuc}}} \text{mRNA}_{\text{cyt}}(t, x) dS - \text{mRNA}_{\text{nuc}}(t) \right) \end{aligned}$$

$$\partial_t \text{mRNA}_{\text{cyt}}(t, x) = D_{\text{mRNA}} \Delta \text{mRNA}_{\text{cyt}}(t, x)$$

$$\begin{aligned} \partial_t \text{CYP3A4}(t, x) = & D_{\text{CYP3A4}} \Delta \text{CYP3A4}(t, x) + k_{\text{cyp}} \text{mRNA}_{\text{cyt}}(t, x) \\ & - k_{\text{cyp}, \text{deg}} \text{CYP3A4}(t, x). \end{aligned}$$

with additional variables

PXR = Free (unbound) PXR concentration

mRNA_{nuc} = mRNA concentration in the nucleus

mRNA_{cyt} = mRNA concentration in the cytoplasm

A mixed PDE/ODE model for the action of Rifampicin

and additional parameters

- v_{ext} = volume of exterior compartment
- σ_{ext} = surface of cell exposed to the exterior compartment
- D_S = diffusion coefficient (or matrix) for substance S in the cytoplasm
- σ_{nuc} = surface of the nucleus
- $k_{mRNA,nuc}$ = first order transcription rate constant for mRNA in the nucleus
- k_{nuc} = first order transport coefficient for mRNA from nucleus to cytoplasm

The boundary conditions for the cytoplasm are, with the boundary of the cytoplasm consisting of the exterior boundary Γ_{ext} and the boundary with the nucleus Γ_{nuc} :

$$\begin{aligned}D_{int} \partial_n X_{int}(t, x) &= 0 \quad \text{on } \Gamma_{nuc} \\D_{int} \partial_n X_{int}(t, x) &= \frac{k_{imp}}{\sigma_{ext}} X_{ext}(t) - \frac{k_{exp}}{\sigma_{ext}} X_{int}(t, x) \quad \text{on } \Gamma_{ext} \\D_{PXR} \partial_n PXR(t, x) &= 0 \quad \text{on } \Gamma_{nuc} \cup \Gamma_{ext} \\D_{PR} \partial_n PR(t, x) &= 0 \quad \text{on } \Gamma_{nuc} \cup \Gamma_{ext} \\D_{mRNA} \partial_n mRNA_{cyt}(t, x) &= 0 \quad \text{on } \Gamma_{ext} \\D_{mRNA} \partial_n mRNA_{cyt}(t, x) &= -\frac{k_{nuc}}{\sigma_{nuc}} (mRNA_{cyt}(t, x) - mRNA_{nuc}(t)) \quad \text{on } \Gamma_{nuc} \\D_{CYP3A4} \partial_n CYP3A4(t, x) &= 0 \quad \text{on } \Gamma_{nuc} \cup \Gamma_{ext}\end{aligned}$$

A first simple mixed PDE/ODE model

A first, very simple attempt towards computation of the previous model is to consider only three substances:

- u_1 – the ligand outside the cell
- u_2 – the ligand binded to the receptor in the cytoplasm
- u_3 – the mRNA in the nucleus (here simply activated without transport)

$$u_1' = d(t) - k_1 u_1 - \frac{s_{12}}{v_1} k_{12} (u_1 - \frac{1}{R} u_2)$$

$$u_2' = -k_2 u_2 + \frac{s_{12}}{v_2} k_{12} (u_1 - \frac{1}{R} u_2)$$

$$u_3' = p_3 - k_3 u_3 + p_{23} u_2$$

To add spatial resolution, replace $u_2(t)$ by $\tilde{u}_2(t, x)$, $x \in \Omega$:

$$u_1' = d(t) - k_1 u_1 - \frac{s_{12}}{v_1} \tilde{k}_{12} (u_1 - \frac{1}{R} \int_{\Gamma_{\text{ext}}} \tilde{u}_2 \, dS)$$

$$\frac{\partial}{\partial t} \tilde{u}_2 - D \Delta \tilde{u}_2 = -k_2 u_2 \quad \text{for all } x \in \Omega$$

$$-D \nabla \tilde{u}_2 \cdot \mathbf{n} = -\tilde{k}_{12} (u_1 - \frac{1}{R} \tilde{u}_2) \quad \text{for } x \in \Gamma_{\text{ext}}, \text{ zero otherwise}$$

$$u_3' = p_3 - k_3 u_3 + p_{23} \int_{\Gamma_{\text{nuc}}} \tilde{u}_2 \, dS$$

$\Gamma_{\text{ext}}, \Gamma_{\text{nuc}} \subset \partial\Omega$ represent the interfaces with the other two compartments.

A first simple mixed PDE/ODE model

We assume that Ω is a 1D domain, $\Omega = [0, 1]$. In this case

$$\int_{\Gamma_{\text{ext}}} \tilde{u}_2 \, dS = \tilde{u}_2(t, 0), \quad \int_{\Gamma_{\text{nuc}}} \tilde{u}_2 \, dS = \tilde{u}_2(t, 1), \quad \text{and} \quad \Delta \tilde{u}_2 = \frac{\partial^2}{\partial x^2} \tilde{u}_2.$$

The main idea in solving the above PDE/ODE system is to replace the second derivative in the space variable by finite differences. We create an equidistant mesh $x_0, x_1, \dots, x_{N-1}, x_N$ of $N + 1$ nodes, where $x_0 = 0$ and $x_N = 1$, and obtain a system of $N + 3$ ODEs. Initial conditions are set to be

$$u_1(0) = u_1^{\text{init}}, \quad \tilde{u}_2(0, x) = 0 \quad \forall x \in [0, 1], \quad u_3(0) = p_3/k_3.$$

To solve this system we used two approaches:

- The software ODEPACK developed by Alan Hindmarsh. This leads to the form

$$v'(t) = Av(t) + b(t)$$

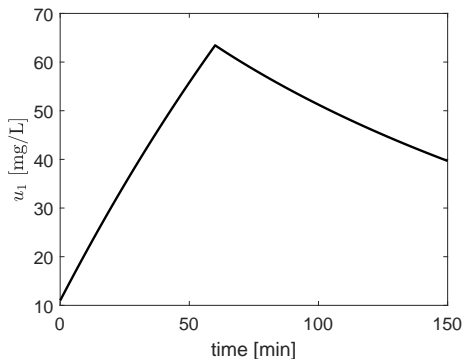
where $v(t) = [u_1(t), \tilde{u}_2(t, x_0), \dots, \tilde{u}_2(t, x_N), u_3(t)] \in \mathcal{R}^{N+3}$, A is a 3-diagonal matrix with model parameters, and $b(t) = [d(t), 0, \dots, 0, p_3] \in \mathcal{R}^{N+3}$.

- Using the Crank-Nicolson scheme. The time derivatives are replaced by finite differences with a time step Δt . This leads to solving a linear system of equations with a 3-diagonal matrix. From the values $v(t)$ we obtain new values $v(t + \Delta t)$.

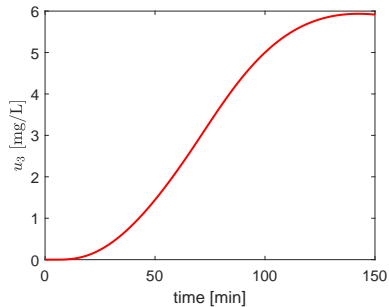
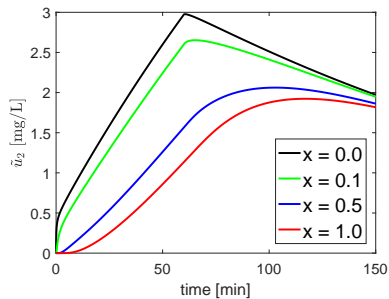
In both cases, we obtained practically the same results.

Simplest PDE/ODE model

The following graphs give consecutively the solutions u_1 , \tilde{u}_2 and u_3 obtained from 1D discretization ($\Omega = [0, 1]$) using finite differences, implemented in Fortran using ODEPACK software. The diffusion D is chosen as the scalar $D = 0.01$, other parameters are taken from the (sometimes fitted) values in the original model.



Simplest PDE/ODE model



There is a clear delay due to the diffusion in the cytoplasm.

Slightly extended PDE/ODE model

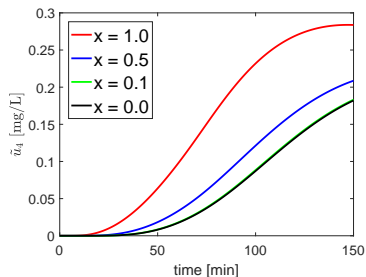
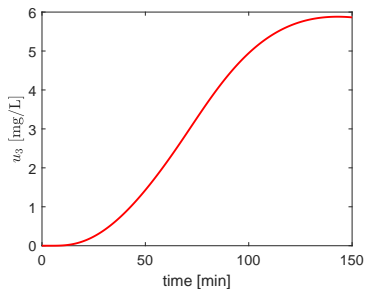
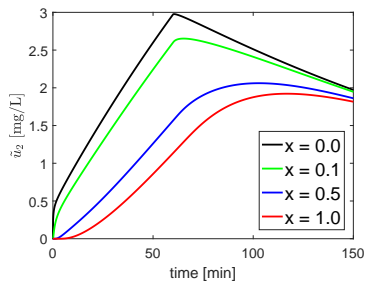
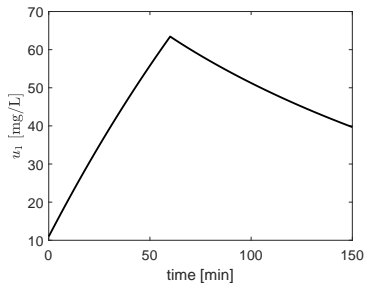
To come closer to the desired model, we can add a fourth substance u_4 representing the mRNA-induced metabolizing enzyme in the cytoplasm. Be aware of the feedback loop - the enzyme metabolizes not only disease-causing substances, but the ligand as well:

$$\begin{aligned}u_1' &= \frac{d(t)}{v_1} - k_1 u_1 - \frac{s_{12}}{v_1} k_{12} (u_1 - u_2) \\u_2' &= -k_2 u_2 - k_{met} u_2 u_4 + \frac{s_{12}}{v_1} k_{12} (u_1 - u_2) \\u_3' &= p_3 - k_3 u_3 + \frac{s_{23}}{v_3} p_{23} u_2 - \frac{s_{23}}{v_3} k_{23} (u_3 - u_4) \\u_4' &= -k_4 u_4 + k_{34} (u_3 - u_4)\end{aligned}$$

Replacing $u_2(t)$ by $\tilde{u}_2(t, x)$ and $u_4(t)$ by $\tilde{u}_4(t, x)$, $x \in \Omega$,

$$\begin{aligned}u_1' &= \frac{d(t)}{v_1} - k_1 u_1 - \frac{s_{12}}{v_1} \tilde{k}_{12} (u_1 - \frac{1}{R_{12}} \int_{\Gamma_{ext}} \tilde{u}_2 dS) \\ \frac{\partial}{\partial t} \tilde{u}_2 - D_2 \Delta \tilde{u}_2 &= -k_2 u_2 - k_{met} \tilde{u}_2 \tilde{u}_4 && \text{for all } x \in \Omega \\ -D_2 \nabla \tilde{u}_2 \cdot \mathbf{n} &= -\tilde{k}_{12} (u_1 - \frac{1}{R_{12}} \tilde{u}_2) && \text{for } x \in \Gamma_{ext}, \text{ zero for } x \in \Gamma_{nuc} \\ u_3' &= p_3 - k_3 u_3 + \frac{s_{23}}{v_3} p_{23} \int_{\Gamma_{nuc}} \tilde{u}_2 dS - \frac{s_{23}}{v_3} k_{23} (u_3 - \frac{1}{R_{34}} \int_{\Gamma_{nuc}} \tilde{u}_4 dS) \\ \frac{\partial}{\partial t} \tilde{u}_4 - D_4 \Delta \tilde{u}_4 &= -k_4 \tilde{u}_4 && \text{for all } x \in \Omega \\ -D_4 \nabla \tilde{u}_4 \cdot \mathbf{n} &= -\tilde{k}_{23} (u_3 - \frac{1}{R_{34}} \tilde{u}_4) && \text{for } x \in \Gamma_{nuc}, \text{ zero for } x \in \Gamma_{ext}\end{aligned}$$

Slightly extended PDE/ODE model



Mixed PDE/ODE models


The main mathematical and numerical challenges with a mixed PDE/ODE model are:

- Correct PDE-formulation of the processes, existence, uniqueness, stability of the (periodic) solution
- Computational costs become an important issue. We need efficient numerical methods for:
 - Time- and space-discretization (finite elements mesh generation)
 - The solution of the discretized nonlinear coupled PDE/ODE model (a (quasi-)Newton type method)
 - The solution of linear systems (Krylov subspace methods, preconditioning, sequences of linear systems)
 - The sum of squares minimization when estimating the parameters (curve fitting)

Recall that during parameter estimation, the model must be run repeatedly!

References


One of very few attempts is this direction:

-  Claus J., Friedmann E., Klingmüller U., Rannacher R., Szekeres T.:
Spatial aspects in the SMAD signaling pathway.
Journal of mathematical biology, vol. 67(5), p. 1171-1197 (2013).

For issues related to coupled PDE/ODE's in this context see also:

-  Carraro T., Friedmann E., Gerecht D.:
Coupling vs decoupling approaches for PDE/ODE systems modeling intercellular signaling.
Journal of computational physics, vol. 314, p. 522-537 (2016).

Related publications:

-  Duintjer Tebbens J., Azar M., Friedmann E., Lanzendörfer M., Pávek P.:
Mathematical Models in the Description of Pregnane X Receptor (PXR)-Regulated Cytochrome P450 Enzyme Induction
International Journal of Molecular Sciences, vol. 19, p. 1785 (2018).
-  Duintjer Tebbens J., Matonoha C., Matthios A., Papáček Š.:
On Parameter Estimation in an In Vitro Compartmental Model for Drug-induced Enzyme Production in Pharmacotherapy
Applications of Mathematics, vol. 64(2), p. 253–277 (2019).

Thank you for your attention.

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